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- (51) International Patent Classification: A61K 9/14, 31/045, 31/075, 31/095, 31/12, 31/13, 47/00 (74) Agent: OHRINER, Kenneth, H.; Lyon & Lyon LLP, 633 West Fifth Street, Suite 4700, Los Angeles, CA 90071-2066 (US).
- (21) International Application Number: PCT/US01/07991 (81) Designated States (national): AU, BR, CA, CN, CZ, FI, HU, IL, JP, MX, NO, NZ, RU, SG.
- (22) International Filing Date: 13 March 2001 (13.03.2001) (84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).
- (25) Filing Language: English (26) Publication Language: English
- (30) Priority Data: 09/528,519 20 March 2000 (20.03.2000) US Published: — with international search report

(71) Applicant: DURA PHARMACEUTICALS, INC. [US/US]; 7475 Lusk Boulevard, San Diego, CA 92121-4204 (US). For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventor: WARD, Gary; 7475 Lusk Boulevard, San Diego, CA 92121-4204 (US).



WO 01/70198 A1

(54) Title: STABILIZED DRY POWDER FORMULATIONS

(57) Abstract: A dry powder formulation for treatment of pulmonary conditions, via inhalation, includes an effective amount of formoterol or a salt or solvate thereof, in a dry powder form, an effective amount of fluticasone, in a dry powder form, and an excipient. A method for preparing a physically stable dry powder formulation for inhalation includes the steps of micronizing a first active polar drug, a second active non-polar drug, and a polar excipient. The second non-polar active drug is first blended with the excipient to form an intermediate mixture. The intermediate mixture is then blended with the first active polar drug. The increased separation of the polar drug and polar excipient stabilizes the formulation.

DESCRIPTION

STABILIZED DRY POWDER FORMULATIONS

5

FIELD OF THE INVENTION

This invention relates to stabilized dry powder formulations used for treatment of respiratory conditions, such as asthma. The invention further relates to the use of a polar bronchodilator in combination with a less polar anti-inflammatory drug for treating respiratory conditions.

10

BACKGROUND OF THE INVENTION

~~Within the past 30 years, asthma has become increasingly prevalent, especially~~
among children. Despite asthma drug therapy, asthma is still a serious and potentially fatal disease. Asthma is now recognized as a chronic inflammatory disease. A common
15 cause for asthma attacks is poor compliance with long-term treatments, such as inhaled steroids. These do not provide immediate relief. On the other hand, patients will readily take bronchodilators using inhalers, since these provide rapid relief of symptoms.

Fluticasone propionate [(6 alpha, 11 beta, 16 alpha, 17 alpha)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester] is an anti-inflammatory drug. It has been used to reduce inflammation
20 in airways. As a nasal spray it is used for rhinitis or inflammation of the nose. It has been used in inhalers for breathing problems like asthma, chronic bronchitis or emphysema.

Fluticasone propionate (referred to herein simply as "fluticasone") is a steroid which reduces the inflammation of nasal passages or bronchial tissue to make breathing
25 easier. Its mechanism of the anti-inflammatory activity in general, is unclear. However, it is thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It has been postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from
30 membrane phospholipids by phospholipase A₂. Chemically, fluticasone propionate is C₂₅H₃₁F₃O₅S. It is non-polar and insoluble in water.

Formoterol fumarate, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-

methylethyl]amino]ethyl]phenyl]formamide), (referred to herein as "formoterol") is a long acting beta agonist which selectively stimulates β_2 -receptors. It is a bronchodilator which relaxes the bronchial smooth muscle, making breathing easier. Inhaled formoterol acts rapidly, usually within minutes. Inhaled formoterol also exerts a prolonged
5 bronchodilation, which in clinical trials has been demonstrated for up to 12 hours. Formoterol is polar and is soluble in water.

Most bronchodilators have relatively short duration of action. By using a compound with long duration e.g. formoterol, with an anti-inflammatory, such as fluticasone, improved therapy can be realized.

10 With these and other powder formulation drugs, physical stability is often difficult to maintain, when the powder is exposed to humidity in the environment, typically after

the powder or dose container is removed from its sealed pouch or package. In the presence of water vapor, active powder drug particles used for inhalation, which are preferably in the 1-10 micron range, tend to fuse together into larger particles. As this occurs, the
15 respirable dose is reduced, because the larger particles deposit out on the mouth, throat, or bronchi, and do not reach the deeper lung. This fusing of particles may occur more rapidly, and with greater detrimental effect, when the formulation has active and excipient particles, (or two or more types of active drug particles) which are both polar, or which are both non-polar.

20

STATEMENT OF THE INVENTION

A dry powder formulation of formoterol, or a physiologically acceptable salt or solvate of formoterol, and fluticasone is delivered to the lung by inhalation. The
25 formulation has higher efficiency and duration of bronchodilator action, as well as a rapid onset of action. This improves compliance for patients. Compliance is simplified as both drugs are delivered in a single dose, with a single dry powder inhaler. The rapid onset of the formoterol gives the patient immediate confirmation that a dose has been delivered. Overdosing is therefore reduced.

30 A dry powder inhaler provides a combined dose of formoterol and fluticasone for inhalation, to treat asthma or other respiratory conditions. Formoterol is polar and is soluble in water. Fluticasone is less polar or non-polar and is insoluble in water. Lactose,

as a preferred excipient, is also polar. A more stable formulation is achieved by micronizing both the formoterol and the fluticasone. The lactose and fluticasone are then blended. This saturates the surface of the relatively larger polar lactose particles with the smaller and non-polar fluticasone particles. The active high energy sites on the lactose particles are largely occupied then by non-polar fluticasone particles. This blended mixture is then blended with the micronized formoterol particles. The physical stability of the resulting formulation is improved because the active particles are more physically separated from each other. Their propensity to fuse together is reduced, so that clumping, caking, or other formation of undesirable large agglomerations is reduced. The polar formoterol particles, which ordinarily would tend to fuse with the polar lactose particles, in the presence of water vapor in the environment, are inhibited from doing so, as they are separated from the high energy sites on the lactose particles by the previously blended in fluticasone. With formulations where there are more than one active drug, the most polar is first blended with the least polar, and then that blended combination is further blended with the remaining active drugs of moderate polarity.

This principle of preparing a stabilized formulation applies equally as well to other drug formulations having at least one more polar and at least one less polar active component.

A method of treating respiratory conditions includes the steps of, delivering, by inhalation of effective amounts of formoterol, or a salt or solvent of formoterol, and fluticasone.

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalenecarboxylate or oleate. These are referred to herein simply as "formoterol". Formoterol is preferably used in the form of its fumarate salt and as a dihydrate.

The ratio of formoterol to fluticasone is preferably within the range of 1:4 to 1:70.

The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 5 to 100 mcg with a preferred dose of 5-50 mcg and

the suitable daily dose for fluticasone **10-100 mcg**, and preferably **30-70 mcg**.

A diluent or carrier, generally non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powder formulation. Lactose is preferred as a carrier for
5 inhaled formulations. The lactose is not micronized. The lactose particles are larger than micronized particles, e.g., larger than 10, 20, or 50 microns.

In preparing the formulation, formoterol fumarate dihydrate and fluticasone are micronized and mixed in the proportions given above. The optionally with the fluticasone blended with an excipient mixture is filled into a powder storage device, such as blister
10 disks or cassettes, as described in U.S. Patent Nos. 5,577,497 and 5,622,166.

The invention provides a mixing rule or process which improves formulation stability.

CLAIMS

1. A dry powder formulation for treatment of pulmonary conditions, via inhalation, comprising:
 - 5 an effective amount of formoterol or a salt or solvate thereof, in a dry powder form;
 - an effective amount of fluticasone, in a dry powder form; and
 - an excipient, in a dry powder form.
- 10 2. The formulation of claim 1 where the molar ratio of the formoterol component to the fluticasone component ranges from 1:2 to 1:100.

3. The formulation of claim 2 wherein the molar ratio ranges from 1:4 to 1:60.
- 15 4. The formulation of claim 1 wherein the excipient comprises lactose.
5. The formulation of claim 1 where the formoterol component comprises fumarate dihydrate.
- 20 6. The formulation of claim 4 wherein the excipient is not micronized and has a particle size substantially greater than the formoterol or the fluticasone.
7. A method for preparing a dry powder formulation for inhalation, comprising the sequential steps of:
 - 25 micronizing a first active polar drug, and a second active non-polar drug;
 - blending the second non-polar active drug with a polar and non-micronized excipient to form an intermediate mixture; and
 - blending the intermediate mixture with the first active polar drug.
- 30 8. A method for preparing a dry powder drug formulation having active components of varying polarity, and an excipient more polar than any of the active components, comprising the steps of:

micronizing each of the active components;

blending the least polar active component with excipient, to form a first intermediate mixture;

determining the absolute value of the polarity of the remaining active components,
5 and ranking them in descending order, from highest to lowest absolute value;

blending the first intermediate mixture with the active component having the greatest absolute value, to form a second intermediate mixture; and

blending the second intermediate mixture with the active component having the next greatest absolute value.

10

9. The method of claim 8 further including the steps of taking the component
~~having the next lowest absolute value, and blending it to make yet another~~
intermediate mixture, until all of the components are blended.

15

10. The method of claim 9 wherein the excipient comprises un-micronized lactose.

11. A dry powder formulation for inhalation into the lung, comprising:
an effective amount of formoterol or a salt or solvate thereof, in a dry
powder form; and

20

an effective amount of fluticasone, in a dry powder form.

International application No.

A. CLASSIFICATION OF SUBJECT MATTER

US CL : 424/489,499;514/579,646,656,657,675,690,691,706,712,715,716,717,724,727,738,777

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/489,499;514/579,646,656,657,675,690,691,706,712,715,716,717,724,727,738,777

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

• **Special categories of cited documents:**

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/07991

Continuation of B. FIELDS SEARCHED Item 3: STN/CASE, WEST

Search terms: formoterol, fluticasone, lactose, formoterol fumarate dihydrate, polar, non-polar

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30 membrane phospholipids by phospholipase A₂. Chemically, fluticasone propionate is C₂₅H₃₁F₃O₅S. It is non-polar and insoluble in water.

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~~the powder or dose container is removed from its sealed pouch or package. In the presence~~
of water vapor, active powder drug particles used for inhalation, which are preferably in the 1-10 micron range, tend to fuse together into larger particles. As this occurs, the
15 respirable dose is reduced, because the larger particles deposit out on the mouth, throat, or bronchi, and do not reach the deeper lung. This fusing of particles may occur more rapidly, and with greater detrimental effect, when the formulation has active and excipient particles, (or two or more types of active drug particles) which are both polar, or which are both non-polar.

20

STATEMENT OF THE INVENTION

A dry powder formulation of formoterol, or a physiologically acceptable salt or solvate of formoterol, and fluticasone is delivered to the lung by inhalation. The
25 formulation has higher efficiency and duration of bronchodilator action, as well as a rapid onset of action. This improves compliance for patients. Compliance is simplified as both drugs are delivered in a single dose, with a single dry powder inhaler. The rapid onset of the formoterol gives the patient immediate confirmation that a dose has been delivered. Overdosing is therefore reduced.

30 A dry powder inhaler provides a combined dose of formoterol and fluticasone for inhalation, to treat asthma or other respiratory conditions. Formoterol is polar and is soluble in water. Fluticasone is less polar or non-polar and is insoluble in water. Lactose,

as a preferred excipient, is also polar. A more stable formulation is achieved by micronizing both the formoterol and the fluticasone. The lactose and fluticasone are then blended. This saturates the surface of the relatively larger polar lactose particles with the smaller and non-polar fluticasone particles. The active high energy sites on the lactose particles are largely occupied then by non-polar fluticasone particles. This blended mixture is then blended with the micronized formoterol particles. The physical stability of the resulting formulation is improved because the active particles are more physically separated from each other. Their propensity to fuse together is reduced, so that clumping, caking, or other formation of undesirable large agglomerations is reduced. The polar formoterol particles, which ordinarily would tend to fuse with the polar lactose particles, in the presence of water vapor in the environment, are inhibited from doing so, as they are separated from the high energy sites on the lactose particles by the previously blended in fluticasone. With formulations where there are more than one active drug, the most polar is first blended with the least polar, and then that blended combination is further blended with the remaining active drugs of moderate polarity.

This principle of preparing a stabilized formulation applies equally as well to other drug formulations having at least one more polar and at least one less polar active component.

A method of treating respiratory conditions includes the steps of, delivering, by inhalation of effective amounts of formoterol, or a salt or solvent of formoterol, and fluticasone.

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalenecarboxylate or oleate. These are referred to herein simply as "formoterol". Formoterol is preferably used in the form of its fumarate salt and as a dihydrate.

The ratio of formoterol to fluticasone is preferably within the range of 1:4 to 1:70.

The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 5 to 100 mcg with a preferred dose of 5-50 mcg and

the suitable daily dose for fluticasone 10-100 mcg, and preferably 30-70 mcg.

A diluent or carrier, generally non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powder formulation. Lactose is preferred as a carrier for
5 inhaled formulations. The lactose is not micronized. The lactose particles are larger than micronized particles, e.g., larger than 10, 20, or 50 microns.

In preparing the formulation, formoterol fumarate dihydrate and fluticasone are micronized and mixed in the proportions given above. The optionally with the fluticasone blended with an excipient mixture is filled into a powder storage device, such as blister
10 disks or cassettes, as described in U.S. Patent Nos. 5,577,497 and 5,622,166.

The invention provides a mixing rule or process which improves formulation stability.

CLAIMS

1. A dry powder formulation for treatment of pulmonary conditions, via inhalation, comprising:
 - 5 an effective amount of formoterol or a salt or solvate thereof, in a dry powder form;
 - an effective amount of fluticasone, in a dry powder form; and
 - an excipient, in a dry powder form.
- 10 2. The formulation of claim 1 where the molar ratio of the formoterol component to the fluticasone component ranges from 1:2 to 1:100.

3. The formulation of claim 2 wherein the molar ratio ranges from 1:4 to 1:60.
- 15 4. The formulation of claim 1 wherein the excipient comprises lactose.
5. The formulation of claim 1 where the formoterol component comprises fumarate dihydrate.
- 20 6. The formulation of claim 4 wherein the excipient is not micronized and has a particle size substantially greater than the formoterol or the fluticasone.
7. A method for preparing a dry powder formulation for inhalation, comprising the sequential steps of:
 - 25 micronizing a first active polar drug, and a second active non-polar drug;
 - blending the second non-polar active drug with a polar and non-micronized excipient to form an intermediate mixture; and
 - blending the intermediate mixture with the first active polar drug.
- 30 8. A method for preparing a dry powder drug formulation having active components of varying polarity, and an excipient more polar than any of the active components, comprising the steps of:

micronizing each of the active components;

blending the least polar active component with excipient, to form a first intermediate mixture;

determining the absolute value of the polarity of the remaining active components,
5 and ranking them in descending order, from highest to lowest absolute value;

blending the first intermediate mixture with the active component having the greatest absolute value, to form a second intermediate mixture; and

blending the second intermediate mixture with the active component having the next greatest absolute value.

10

9. The method of claim 8 further including the steps of taking the component
having the next lowest absolute value, and blending it to make yet another
intermediate mixture, until all of the components are blended.

15

10. The method of claim 9 wherein the excipient comprises un-micronized lactose.

11. A dry powder formulation for inhalation into the lung, comprising:
an effective amount of formoterol or a salt or solvate thereof, in a dry
powder form; and

20

an effective amount of fluticasone, in a dry powder form.

International application No.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14, 31/045, 31/075, 31/095, 31/12, 31/13, 47/00

US CL : 424/489,499;514/579,646,656,657,675,690,691,706,712,715,716,717,724,727,738,777

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/489,499;514/579,646,656,657,675,690,691,706,712,715,716,717,724,727,738,777

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,955,439 A (GREEN) 21 September 1999 (21.09.1999), column 2, lines 3-65, column 7, column 8, lines 1-28, column 9, lines 51-68, columns 10-12, claims 1-31.	1-7, 11

<input type="checkbox"/> Further documents are listed in the continuation of Box C.	<input type="checkbox"/> See patent family annex.
<p>Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>Date of the actual completion of the international search</p> <p>08 May 2001 (08.05.2001)</p> <p>Name and mailing address of the ISA/US</p> <p>Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231</p> <p>Facsimile No. (703)305-3230</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> <p>Date of mailing of the international search report</p> <p>04 JUN 2001</p> <p>Authorized officer</p> <p>JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX</p> <p>Frank Choi <i>Frank Choi</i></p> <p>Telephone No. (703) 308-1235</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/07991

Continuation of B. FIELDS SEARCHED Item 3: STN/CASE, WEST

Search terms: formoterol, fluticasone, lactose, formoterol fumarate dihydrate, polar, non-polar